REMARKS

Applicant requests reconsideration of the present application in view of the following comments.

I. Status of the Claims

Claims 1, 11-13, 41, 42 and 44 have been amended. Support for the amendments can be found for example at US 2002/0065397, ¶¶ [0085], [0088], Example 6 and original claim 1.

Per Examiner Schnizer's recommendation, applicant has renumbered claims 23-40 as "new" claims 47-64 and designated them as "New-Withdrawn". Thus, claims 23-40 have been cancelled, and claims 47-64 are withdrawn.

Claims 7-10, 14-16, 43 and 45-46 also have been cancelled.

Upon entry of these amendments, therefore, claims 1-6, 11-13, 17-22, and 41-42 and 44 will be pending.

II. Finality of Office Action

Applicant again requests reconsideration of the finality of the pending action in the above-referenced case. The action asserts a new obviousness rejection based on Boos *et al.*, a publication not previously cited.

There is no justification proffered for advancing a new line of argument in a "final" action. Certainly, nothing about applicant's last claim revisions necessitated the new rejection. To the contrary, the examiner's rationale for invoking Boos bears no apparent relationship to applicant's most recent claim amendments, which simply echo themes already acknowledged by the USPTO in this case. *See* Board Decision of March 26, 2008 (reversing previous obviousness rejection), for example, at page 8.

When he issued the June 6th Office Action, furthermore, the examiner already had considered substantially the same claim in U.S. SN 12/041908 (*See* claim 1), a

continuation of the instant case, as applicant entered here in its December 4th response (*See* claim 1).

Accordingly, the examiner reasonably could have expected that the recitations at issue here would appear in claims of the instant application. *See* MPEP § 706.07(a) ("...any subsequent action on the merits ... should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be claimed").

In fact, applicant's identification of the examiner's failure to establish a requisite motivation to have combined previously cited prior art appears to have been the examiner's inspiration for issuing a new rejection. *See* Office Action dated February 20, 2009, at page 13. Yet, this cannot justify a final action as the vehicle for a new rejection and a related new line of argument over patentability.

Accordingly, the pending action should be reissued as "non-final." In any event, the examiner should enter the present claim revisions since (A) they represent applicant's first opportunity in the present prosecution to address new grounds for rejection, mentioned above, and (B) the revisions significantly simply the issues for appeal, *e.g.*, under Section 112.

III. Rejections Under 35 U.S.C. § 112

The examiner rejects claims 1-13, 17-22, 41, 42, and 44 for alleged indefiniteness. In one aspect, the examiner asserts that the antecedent for the term "said immunocompetent subject," as a source of blood samples, somehow is unclear.

Applicant would emphasize, however, that the specification leaves no doubt that first and second modified therapeutic agents can be evaluated in the same or different subjects. *See, e.g.*, US 2002/0065397 at [0085], [0088], Example 6, and original claim 1. Accordingly, the skilled person informed by this specification would recognize immediately that the phrase "immunocompetent subject" refers to the person or persons from whom blood samples were assayed.

Although the claims in question thus admit to no significant ambiguity, applicant has endeavored to advance prosecution by revising claims 1, 41, 42 and 44 to identify specifically the person associated with each sample. These changes are believed to obviate the stated basis for this rejection.

In another aspect, the examiner asserts that recitation of the term "such as" renders the claims indefinite. Applicant has deleted this phrase from the claims, mooting the rejection.

IV. Rejections Under 35 U.S.C. § 103

The examiner newly rejects claims 1-3, 5-7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, and Francis *et al.* The examiner also rejects claim 4 over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Petersen. The examiner rejects claims 8, 11, and 20-22 over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Abuchowski *et al.* The examiner rejects claim 19 as well over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Bollin. Applicant traverses these rejections.

Apparently recognizing the shortcomings of the rationale for obviousness advanced previously, the examiner newly cites Boos for allegedly "providing a template for comparing different preparations of asparaginase," thereby supplying a motivation for the skilled artisan to use enzymatic activity as the metric by which to optimize the protection of an enzymatic therapeutic agent against host-mediated inactivation. *See* Final Office Action at page 7. In so doing, the examiner presumes the very insight that applicant's own disclosure provided. Such a presumption is the hallmark of hindsight reconstruction and cannot support a prima facie case of obviousness. *In re Sang Su Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002) ("It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to '[use] that which the inventor taught against its teacher'"), *citing W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

According to the examiner, "Boos studied the effects of using *unmodified* asparaginase from *different* sources, (*E. coli* or *Erwinia*) in the *treatment* of acute

lymphoblastic leukemia because it was known that different asparaginase preparations had pharmacokinetic differences associated with increasing reports of hemorrhagic and thrombotic events." *Id.* at 4 (emphasis added). In particular, Boos evaluated the known variability in activity among different commercial preparations of asparaginase by monitoring, among other things, asparaginase activity during the course of therapy of 56 children and, thereby, formulated dosing recommendations for each commercial preparation. For instance, *see* Boos *et al.* at page 1545, column 1, in the 1st full paragraph, and at page 1549. Beyond asparaginase activity, Boos measured "asparagine levels, as the main biochemical parameter of the desired therapeutic effect, and the aspartic acid concentration and levels of glutamine and glutamic acid, as parameters potentially associated with toxic side-effects." *Id.* at page 1545, column 1, in the 1st full paragraph.

It is hardly surprising that a practitioner formulated dose-response curves in an effort to formulate a uniform dosing regime for an enzymatic therapy. Nothing in the cited materials, however, suggests that such testing should be applied in the preclinical setting of research and development, as the examiner contends. Indeed, the examiner's assertion about what a skilled person conceivably might have been motivated to do in a preclinical setting belies what artisans before the present invention actually did.

From the various documents cited previously against the claimed invention, such as Chinol *et al.*, Deckert *et al.* and Alvarez *et al.*, it is clear that practitioners in the relevant field, circa 2000, sought to optimize therapeutic agents against host-mediated inactivation by examining the impact of antigenicity, immunogenicity, and acceptable loss of bioactivity. *See also* Appeal Brief, filed November 10, 2006, at pg. 2-5 and 10-13. Thus, conventional wisdom regarding therapeutic protein optimization focused upon shielding the therapeutic protein from the immune system and increasing the protein's stability. *See* US 2002/0065397 at ¶¶ [0002] to [0007], *inter alia*.

By the same token, it was applicant's insight to abandon convention and optimize the modification a therapeutic enzyme by evaluating the modified enzyme's capacity to catalyze its reaction. Now, the examiner attempts to use that very insight against applicant to suggest a basis for why one of ordinary skill might have combined the cited references. Such a *post*

hoc rationale cannot support a *prima facie* case of obviousness, however. *See In re Sang Su Lee*, 277 F.3d at 1344.

Furthermore, the examiner cherry-picks from among the cited references various steps used to determine the modification conditions of a therapeutic agent from among countless possible combinations. Nothing in the cited record, however, suggests which parameters are critical or which of many possible choices is likely to be successful for determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation of the therapeutic agent. Thus, nothing in the cited material would have guided an artisan contemplating a method of determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation to a method specifically measuring biological activity as claimed.

As noted previously, the examiner's *post hoc* approach mirrors those condemned by the Federal Circuit in *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), and in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008). In reply, the examiner asserts that the cited *Takeda* and *Ortho-McNeil* cases have no bearing on the instant case allegedly because the claims at issue therein concerned "compositions," whereas the instant claims concern "methods."

That the examiner cites neither case law nor PTO rule for this distinction is unsurprising, since there is no precedent for treating method claims and composition claims differently in this context. Indeed, save for unrelated provisions concerning "biotechnological processes," Section 103 speaks only of "the subject matter sought to be patented," *sans* any sort of method/composition delineation, in mandating the elements of a proper obviousness analysis. Suffice to say, therefore, that the examiner's rationale for denying here the relevance of *Takeda* and *Ortho-McNeil* is wholly without foundation and therefore improper.

A *prima facie* case obviousness has not been established. Accordingly, applicant requests withdrawal of the pending Section 103 rejections.

CONCLUSION

Applicant submits that this application is in condition for allowance, and an early indication to this effect is requested. Examiner Schnizer also is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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